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Preservative-free versus preserved latanoprost eye drops for reducing intraocular pressure: a non-inferiority phase III randomized, multi-center, single-blind, parallel-group controlled trial

Panos Theodosiadis [1], Anastasios Konstas [2], Ioannis Halkiadakis [3], Vasiliki Dimera [4], Dimitrios Koufakis [5], Constantinos D Georgakopoulos [6], Evgenia Kanonidou [7], Elias Zintzaras [8], Konstantina Soulele [9], Antonios Margaritis [9], Lida Kalantzi [9]

[1] Attikon University Hospital, Athens, Greece
[2] General University Hospital of Thessaloniki AHEPA, Thessaloniki, Greece
[3] Ophthalmiatreio Athens, Athens, Greece
[4] General Hospital of Larissa, Larissa, Thessaly, Greece
[5] IASO Thessalias, Larissa, Greece
[6] General University Hospital of Patra, Patra, Greece
[7] General Hospital of Thessaloniki Ippokrateio, Thessaloniki, Greece
[8] BECRO, Athens, Greece
[9] Pharmathen S.A., Attica, Greece

ABSTRACT

Background: The aim of this study was to test the non-inferiority of preservative-free (PF) latanoprost 50 µg/mL multi-dose ophthalmic solution versus the marketed benzalkonium chloride (BAK)-preserved latanoprost 50 µg/mL ophthalmic solution in patients with open-angle glaucoma and patients with ocular hypertension.

Methods: This was a prospective, national, randomized, multi-center, observer-blind, parallel-group controlled clinical trial. Patients were randomized to receive either PF or BAK-preserved latanoprost once daily for 12 weeks. The primary endpoint was the change in intraocular pressure (IOP) at 8:00 AM in the affected eye between the end of the treatment (week 12) and the baseline (week 0). Secondary measurements were taken at weeks 2 and 6, with IOP being recorded at 8:00 AM, 12:00 PM, and 4:00 PM.

Results: A total of 158 patients were included in the per protocol (PP) population (77 in the PF latanoprost treatment arm and 81 patients in the BAK-preserved latanoprost treatment arm). PF latanoprost was non-inferior to BAK-preserved latanoprost in reducing IOP at 8:00 AM in the study eye from the baseline (week 0) to the end of the treatment (week 12). The point estimate of the between-treatment difference was 0.1 mmHg (95% confidence interval: -0.646, 0.847). Mean between-group differences in IOP reduction from the baseline to each of the secondary measurements were also similar between the two treatment arms. The two treatments were well tolerated and had comparable adverse event profiles.

Conclusions: PF latanoprost was non-inferior to BAK-preserved latanoprost in reducing IOP in patients with open-angle glaucoma or ocular hypertension. Both treatments were well tolerated.

KEY WORDS

glaucoma, intraocular pressure, benzalkonium chloride, latanoprost, preservative-free, eye drop, randomized controlled trial, preservative-free

Correspondence to: Dr. Lida Kalantzi PhD, Head of Scientific Affairs, Pharmathen S.A., 44, Kifissias Ave., 15125 Marousi Attica, Greece, E-mail: lkalantzi@pharmathen.com

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INTRODUCTION

Latanoprost is a prostaglandin analog that is widely used in the treatment of high intraocular pressure (IOP) in patients with open-angle glaucoma and patients with ocular hypertension [1]. Latanoprost is actually a prodrug: upon instillation onto the cornea, latanoprost is rapidly hydrolyzed by topical esterases in the cornea to provide the pharmacologically active latanoprost acid [2].

One way latanoprost might reduce IOP is an increase in aqueous humor outflow. This pharmacodynamic effect is mediated by two main mechanisms. The first includes the enhancement of the pressure-sensitive trabecular outflow pathway, while the second is mediated through an increase in pressure-insensitive uveoscleral outflow [3, 4]. Following a single dose of latanoprost 0.005% ophthalmic solution, IOP reduction is maximal at 8–12 hours post-instillation, with IOP remaining below the pretreatment levels for at least 24 hours. Thus, latanoprost administered once daily in the evening exerts a sustained IOP reduction, with the hypotensive effect being the greatest during the day [2, 5].

Compared with other prostaglandin analogs, ophthalmic solutions of latanoprost exhibit higher ocular tolerability with fewer adverse events (AEs), indicating a more favorable efficacy and safety profile [6]. Since latanoprost eye drops usually contain a preservative, the impact of latanoprost on the AE profile of the formulation remains controversial [7]. In fact, preservative agents are generally considered to contribute to decreased ocular surface tolerability. Especially in patients receiving chronic treatments or suffering from underlying ocular surface diseases, topical AEs of preserved antiglaucoma medications should be carefully considered, as they may significantly influence patients' compliance and quality of life [6].

Latanoprost is marketed as a 0.005% ophthalmic solution containing 0.02% preservative benzalkonium chloride (BAK) [6]. Efficacy and safety results from previous studies have suggested a similar efficacy and similar or better local tolerance of preservative-free (PF) latanoprost ophthalmic solutions compared with the marketed BAK-preserved formulation, with less conjunctival hyperemia and less subjective symptoms upon instillation (such as burning, stinging, and pruritus) [6, 8-10].

Based on these data, the industry responded positively to addressing the needs of patients with sensitivity or allergy to BAK, with a number of single-dose PF antiglaucoma formulations approved during the last years [11, 12]. However, the use of single-dose packages can have a higher cost and may also be proven problematic in a subset of patients, such as in the elderly with decreased manual dexterity, which increases the potential for microbial contamination [13, 14].

To accommodate this unmet patient need, a new, multi-dose, PF latanoprost 50 μg/mL eye drops solution (Pharmathen S.A., Athens, Greece) has been developed, which is user-friendly and, at the same time, capable of maintaining a high product quality. The product is packaged in a novel multi-dose container with the Aero Pump 3K technology, which offers a three-part contamination protection: a specially designed filter that protects the product from microbiological contamination by using the enclosed air necessary for volume equalization, a silver spiral on the upper fraction to hinder bacterial growth, and a special valve system that stops backflow.

Therefore, the aim of this study was to assess the non-inferiority of this new PF formulation versus the BAK-preserved product (Xalatan) in reducing IOP in patients with open-angle glaucoma and patients with ocular hypertension over a 12-week treatment period.

METHODS

Study design and participants

This was a national, randomized, multi-center, observer-blind, parallel-group controlled phase III clinical trial comparing PF latanoprost 50 μg/mL multi-dose ophthalmic solution (Pharmathen S.A., Athens, Greece) with BAK-preserved latanoprost 50 μg/mL (Xalatan; Pfizer Limited, Kent, UK). Due to differences in the medication packaging (PF latanoprost has a special container closure system that uses Aero Pump 3K technology), the investigator measuring the IOP was masked to the study medication. The study was conducted at seven clinical sites in Greece (General University Hospital of Athens Attikon, General University Hospital of Thessaloniki AHEPA, General Hospital of Larissa, Ophthalmiatreio Athens, IASO Thessalias, General University Hospital of Patra, and General Hospital of Thessaloniki Ippokrateio) between October 10, 2017 and February 23, 2018. The study protocol was prospectively approved by the National (Hellenic) Ethics Committee (NEC) (September 15, 2017) and the National (Hellenic) Organization for Medicines (EOF) (September 26, 2017). The current study was conducted in compliance with the Declaration of Helsinki (2004) and Good Clinical Practice (GCP) guidelines. Relevant written informed consent was obtained from the patients prior to study enrollment. The study was registered in the EU Clinical Trials Register

database with trial identification number 2017-002910-29. Eligible subjects were male or female patients (≥18 years old) with unilateral or bilateral open-angle glaucoma or ocular hypertension. Following at least 4 weeks of washout of IOP-lowering medications, at baseline, patients were required to have an average IOP ≥ 22 mmHg and ≤ 35 mmHg in at least one eye and a best-corrected visual acuity ≥ 20/100 (Snellen) corresponding to the logarithm of minimal angle of resolution (logMAR) of 0.7. Patients were eligible for inclusion in the study if IOP was expected by the investigator to remain controlled with the new treatment without optic nerve damage or progression of visual field loss; arterial blood pressure was controllable; and no new systemic medication that may have altered the IOP (e.g., beta-blockers, calcium channel blockers, angiotensin-converting enzyme [ACE] inhibitors, and prostaglandins) had been taken in the previous 30 days. The primary exclusion criteria were a history of chronic and recurrent inflammatory ocular disease, ocular trauma, or infections; a history of anterior chamber lens, torn posterior lens capsule, or corneal abnormalities that would preclude accurate IOP reading with an applanation tonometer; clinically significant or progressive retinal disease; narrow-angle/angle-closure glaucoma; intraocular surgery within the previous 3 months; aphakia or any known risk factor for cystoid macular edema; ocular laser surgery within the previous 1 month; cup/disk ratio > 0.8; best-corrected visual acuity ≤ 20/100 (Snellen), corresponding to worse than 0.7 logMAR score; treatment with topical, ocular, nonsteroidal anti-inflammatory drugs, local or systemic corticosteroids, or oral carbonic anhydrase inhibitors, or any change in systemic medication that affects IOP within the previous 30 days; and a history of allergic hypersensitivity or poor tolerance to any study medication component. Patients who were pregnant, breast-feeding, or of childbearing potential and not protected by a highly effective contraceptive method of birth control were also excluded from the study. The sample size of the participating population was calculated to obtain the required power for the demonstration of non-inferiority of PF latanoprost eye drops (test, T) compared to BAK-preserved latanoprost (control, C) in reducing IOP from baseline. For this calculation, the one-sided significance level was set to 2.5%, and the power was set to 80%. A non-inferiority margin of 1.5 mmHg was used, as this tolerance criterion is usually employed and accepted in non-inferiority glaucoma studies [14-16], assuming a common standard deviation of the between-group difference of 2.6, and a mean difference between the treatment groups of 0.3. With the above assumptions, a total sample size of 150 patients was initially required to be enrolled in the study, equally distributed to the respective treatment groups. Furthermore, since the primary analysis is typically based on the per protocol (PP) population, a dropout rate of approximately 15% was further assumed, leading to a total of 170 patients (i.e., 85 patients per treatment group) being included in the study.

Treatment and efficacy assessments

Eligible patients were randomized at day 0 to receive once-daily treatment with either PF latanoprost 50 µg/mL or BAK-preserved latanoprost 50 µg/mL for a total duration of 12 weeks. Patients were instructed to instill one drop in each eye at approximately in the evening and were scheduled for follow-up visits at weeks 2, 6, and 12. As the clinical trial was observer-blind, due to differences in the medication packaging, to ensure masking, treatment allocation was carried out by personnel other than the observer. Patients were asked at each visit about their compliance with the treatment regimen, and their answers were recorded. To further assess compliance, patients were asked to return full and empty bottles of the eye drops at the end of the clinical trial and to keep a personal diary where the date and time of each instillation was recorded. Patients should bring the diary back at every scheduled visit (weeks 2, 6, and 12).

IOP was measured using a calibrated Goldmann tonometer at 8:00 AM, 12:00 PM, and 4:00 PM (±1 h) at baseline and at weeks 2 (±2 days), 6 (±2 days), and 12 (±4 days). Two consecutive measurements were taken in each eye; if these two measurements differed by more than 4 mmHg, a third measurement was performed. The IOP for a given eye was calculated as the mean of two or three IOP measurements. Diurnal IOP was defined as the mean IOP at all time points during a visit. In patients with bilateral disease, where one of the two eyes satisfied the eligibility criteria (study eye), the contralateral eye was treated with BAK-preserved latanoprost 50 µg/mL, and the study eye was randomly assigned to one of the two study groups. If the criteria for evaluation were fulfilled for both eyes, the eye with the higher IOP at baseline was included.

Safety assessments

Safety evaluations included both ocular and systemic AEs, including a decrease in visual acuity as compared to baseline, changes in ocular signs based on slit-lamp biomicroscopy examination, subjective ocular findings (irritation, stinging, burning, eye dryness, and foreign body sensation), and vital signs (heart rate and blood pressure). The safety population (SP) consisted of all patients receiving at least one eye drop of PF or BAK-preserved latanoprost. Descriptive statistics were used to summarize the safety data (mean and standard deviation). Safety data were also compared, when appropriate, using the chi-square test or Fisher's exact test,

based on the nature of the obtained data. Statistical significance was set at $P < 0.05$. All analyses were performed using IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, NY, USA).

Efficacy endpoints and statistical analyses

The intent-to-treat (ITT) population included all randomized patients who had at least one post-baseline IOP measurement. The PP population included all randomized patients who had no major protocol violations, completed IOP measurements, completed at least 12 weeks of treatment, and did not take prohibited medication. A primary efficacy analysis was performed in the PP population. For collateral purposes, an efficacy assessment was conducted on the ITT population. Missing data were not imputed. The primary efficacy endpoint to prove non-inferiority was the change in IOP at 8:00 AM in the study eye from baseline to the end of the treatment (week 12). Comparison of treatments was performed using an analysis of covariance model (ANCOVA), with treatment as the main effect and baseline IOP as a covariate. The test medication was considered to be non-inferior to the control medication if the upper 95% confidence interval (CI) limit for the difference (T - C) was < ΔNI, where ΔNI = 1.5 mmHg was the defined non-inferiority criterion. This non-inferiority criterion is commonly used and accepted in non-inferiority glaucoma studies [14-16]. The center-by-treatment interaction was included as a fixed effect in the ANCOVA model for the primary endpoint. If the interaction was not significant, it was omitted from the analysis. Secondary efficacy endpoints included changes in IOP from baseline to each follow-up time point (week 12: 12:00 PM and 4:00 PM; weeks 2 and 6: 8:00 AM, 12:00 PM, and 4:00 PM). Secondary efficacy analysis was performed using ANCOVA, with treatment as the main effect and baseline IOP as a covariate. The treatment difference and two-sided 95% CI for the difference were also obtained for the secondary endpoints.

Ancillary statistical analyses in the PP population included ANCOVA to further assess the change in diurnal IOP from baseline to week 12 (with treatment as the main effect and baseline diurnal IOP as covariate). Additionally, a repeated measures general linear model was applied to investigate the trend of IOP over time, with treatment as a between-subjects factor and IOP at baseline, week 2, week 6, and week 12, or diurnal IOP as within-subjects variables. Analyses were performed for IOP measurements at 8:00 AM, 12:00 PM, and 4:00 PM and for the mean diurnal IOP.

RESULTS

Patient distribution and baseline characteristics

A total of 170 patients were randomized into the PF latanoprost group (86 patients) or the BAK-preserved latanoprost group (84 patients) (Figure 1). Of these, 158 patients (77 patients in the PF latanoprost group and 81 patients in the BAK-preserved latanoprost group) were finally included in the PP population. Twelve patients (7.1%; 9 patients in the PF latanoprost group and 3 patients in the BAK-preserved latanoprost group) dropped out of the clinical trial, and the reasons are detailed in Figure 1.

The baseline characteristics of the patients are listed in Table 1. The demographic and clinical characteristics were comparable between the two treatment groups at baseline. The treatment groups showed no statistically significant differences ($P > 0.05$) in terms of demographic and baseline clinical characteristics. All enrolled patients had well-controlled IOP before inclusion in the study. The difference in IOP between the test and control groups at all three baseline measurements at 8:00 AM, 12:00 PM, and 4:00 PM was not significant ($P > 0.05$ for all measurements). Treatment compliance was fairly good: 98.8%, 100%, and 100% for the test medication and 100%, 100%, and 100% for the control medication at weeks 2, 6, and 12, respectively.

Efficacy analysis

The evaluation of non-inferiority of PF latanoprost versus BAK-preserved latanoprost was based on the PP population, as already mentioned. Both treatment groups showed a statistically significant mean decrease from baseline in the study eye IOP at all measured time points. The recorded mean changes in IOP from baseline until the end of the study ranged from -6.51 mmHg to -8.23 mmHg for the PF latanoprost group and from -6.8 mmHg to -8.16 mmHg for the BAK-preserved latanoprost group (Figure 2). Treatment compliance was similar between the two treatment groups.

PF latanoprost was non-inferior to BAK-preserved latanoprost for the primary efficacy endpoint, that is, the change in IOP at 8:00 AM in the study eye from baseline (week 0) to the end of the treatment (week 12). The point estimate of the between-treatment difference was 0.10 mmHg (95% CI: -0.65, 0.85) in the PP population, with the upper limit of the 95% CI not exceeding the non-inferiority margin of 1.5 mmHg (Table 2, Figure 3).

The center-by-treatment interaction was not significant ($P = 0.781$); therefore, it was omitted from the ANCOVA model. Non-inferiority of the two treatments was further confirmed in the ITT population, with the between-treatment difference being 0.08 mmHg (95% CI: -0.681, 0.836) and the upper limit of the 95% CI not exceeding the non-inferiority margin of 1.5 mmHg. Statistically non-significant differences between the two treatment arms in changes in IOP from baseline at all-time points of each visit were further obtained during evaluation of the secondary

efficacy endpoints, which supported the primary efficacy analysis (Table 2). The mean diurnal IOP reductions from baseline to week 12 were also similar between the two treatment arms (Table 2). Ancillary analyses in the PP population performed for IOP measurements at 8:00 AM, 12:00 PM, 4:00 PM and, also, for the diurnal IOP, by means of repeated measures in ANOVA, revealed a statistically significant effect of time (baseline and weeks 2, 6, and 12) ($P < 0.001$), while the treatment effect and the interaction between treatment and time were not significant ($P > 0.05$), indicating that the variability of the treatment effect was consistent over time.

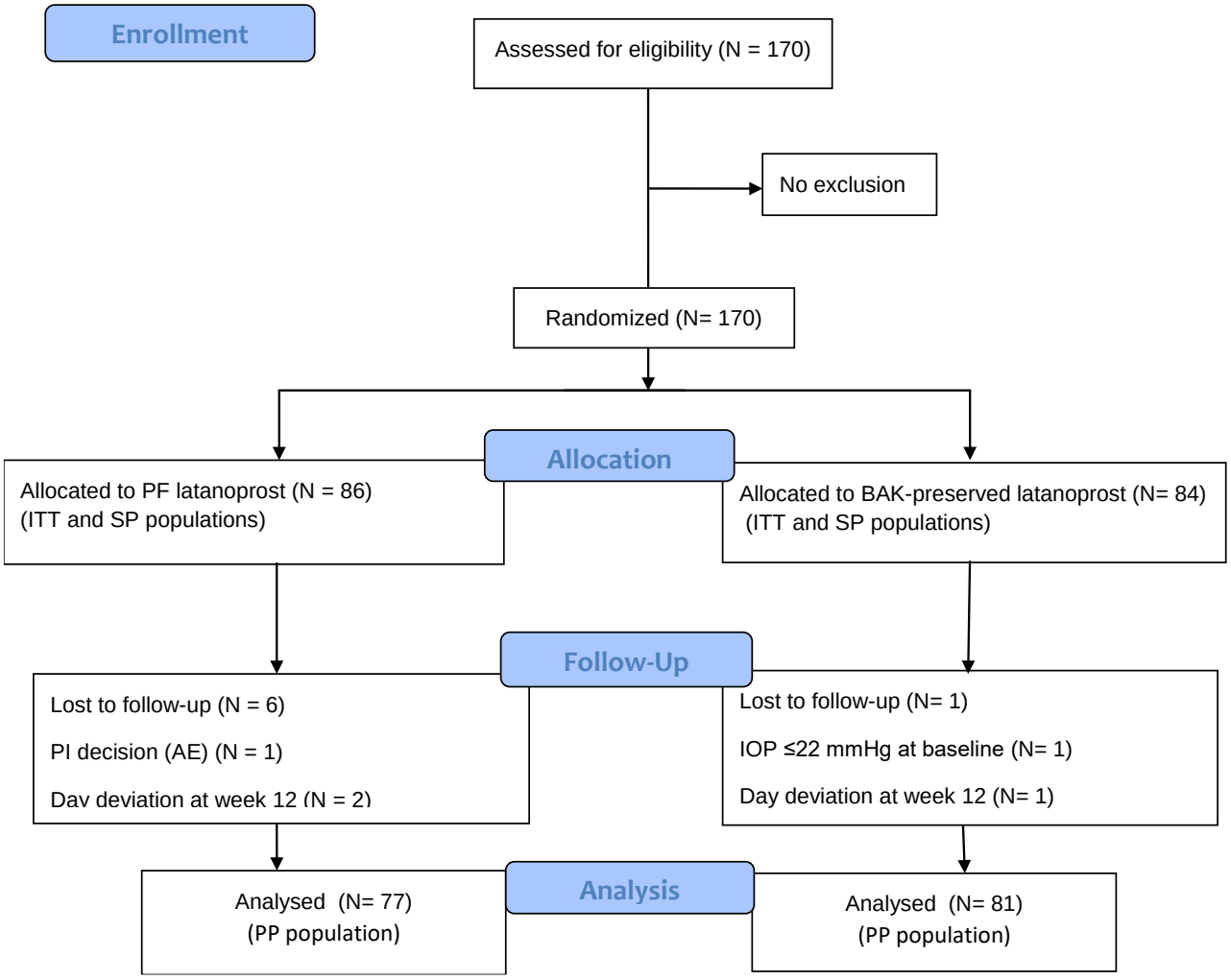

Figure 1. Patient allocation into the PF latanoprost (Pharmathen S.A.) or BAK-preserved latanoprost (Xalatan). Abbreviations: N, number; PF, preservative-free; BAK, benzalkonium chloride; ITT, intent to treat; SP, safety population; PI, principal investigator; AE, adverse event; IOP, intraocular pressure; mmHg, millimeter of mercury; PP, per protocol.

Table 1. Patient demographics and baseline characteristics of the PP population.

	PF latanoprost (N = 77)	BAK-preserved latanoprost (N = 81)	*P*-value
Age, years Mean (SD)	70.1 (9.5)	69.3 (9.2)	0.615
Sex, Woman, n (%)	47 (61.0)	53 (65.4)	0.567
Caucasian, n (%)	77 (100.0)	81 (100.0)	0.999
Open-angle glaucoma, n (%)	55 (71.4)	51 (63.0)	0.258
Bilateral disease (%)	64 (83.1)	65 (80.2)	0.641
Comorbidities, n (%)	62 (80.5)	68 (84.0)	0.572
History of allergies, n (%)	6 (7.8)	4 (4.9)	0.461
Concomitant medications, n (%)	59 (76.6)	67 (82.7)	0.341
History of ocular surgery, n (%)	25 (32.5)	29 (35.8)	0.659
History of ocular laser surgery, n (%)	4 (5.2)	2 (2.5)	0.370
IOP (mmHg) at 8:00 AM [mean (SD)]	24.6 (2.3)	24.2 (1.8)	0.281
IOP (mmHg) at 12:00 PM [mean (SD)]	24.4 (2.0)	24.1 (1.9)	0.424
IOP (mmHg) at 4:00 PM [mean (SD)]	24.0 (2.0)	23.7 (1.9)	0.266
Diurnal mean IOP (mmHg) [mean (SD)]	24.3 (1.9)	24.0 (1.7)	0.281

PP, per protocol; BAK, benzalkonium chloride; n, number; %, percentage; IOP, intraocular pressure; mmHg, millimeter of mercury; PF, preservative-free; SD, standard deviation.

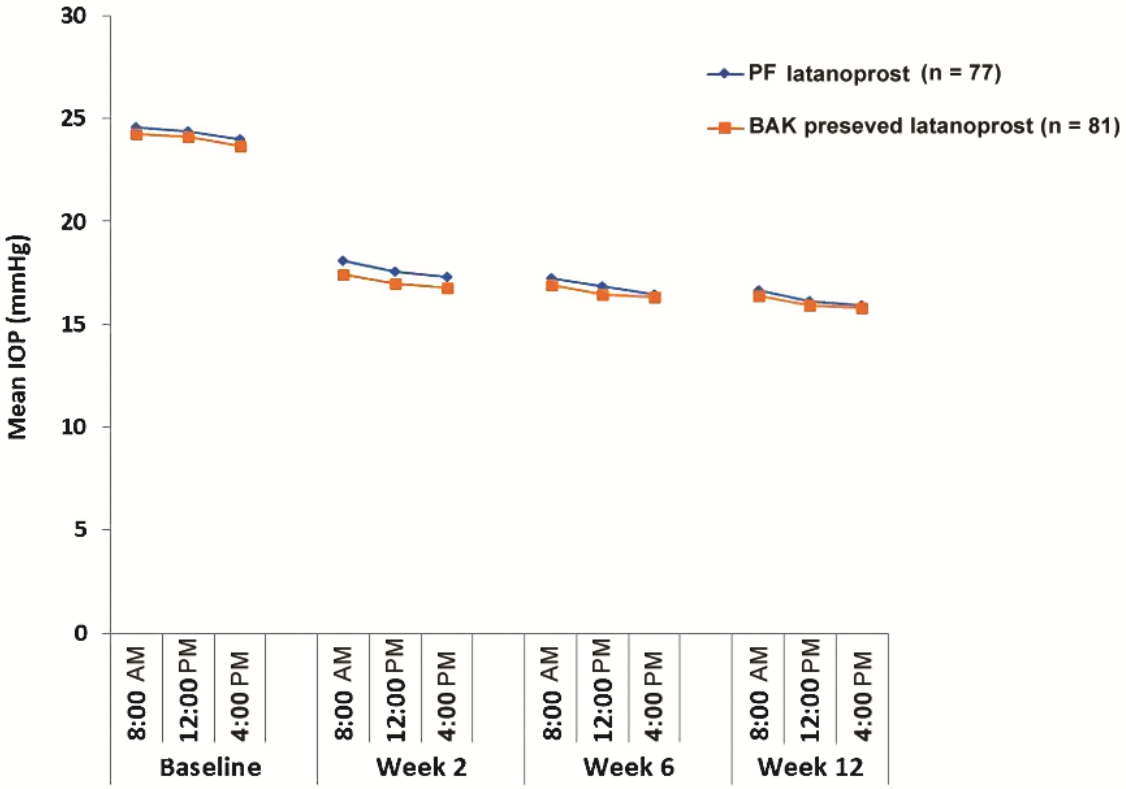

Figure 2. Mean IOP (mmHg) at each assessment time for the per protocol population. Abbreviations: PF, preservative-free; BAK, benzalkonium chloride; N, number; IOP, intraocular pressure; mmHg, millimeter of mercury.

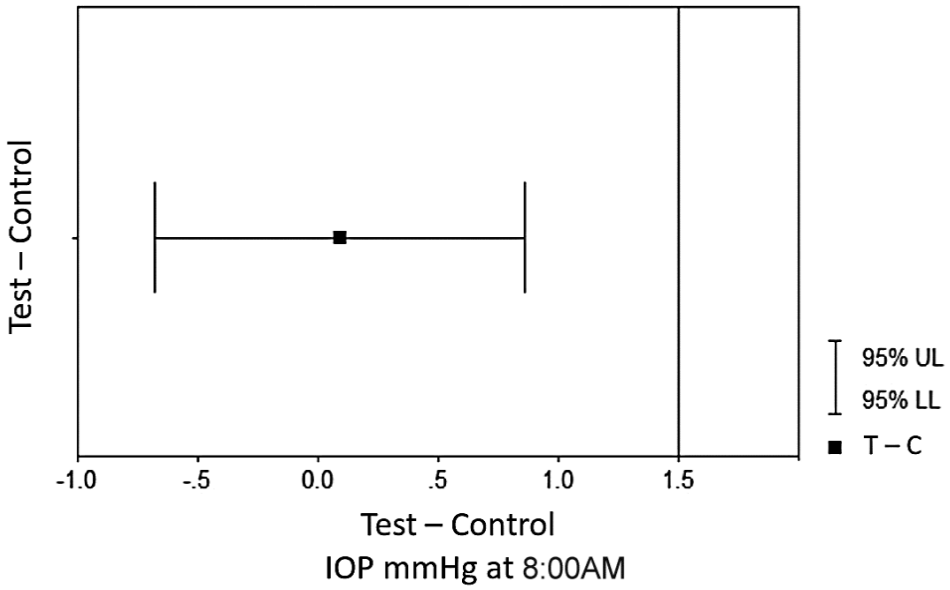

Figure 3. Forest plot showing the mean between-group difference in the change from baseline IOP. The least square mean and 95% confidence interval are presented. C, control; IOP, intraocular pressure; mmHg, millimeter of mercury; LL, lower limit; T, test; UL, upper limit. The medication used in the test group: PF latanoprost (Pharmathen S.A.), and the medication used in the control group: BAK-preserved latanoprost (Xalatan).

Table 2. IOP change and 95% CIs for the difference in IOP from baseline to the pre-specified time points for PF and BAK-preserved latanoprost in the PP population.

Time	Mean ± SD IOP (mmHg)						
Primary efficacy endpoint							
	Baseline		**Week 12**				
	PF	BAK	PF	BAK	Difference [a]	95% CI [b]	*P*-value
8:00 AM	24.59 ± 2.30	24.24 ± 1.77	16.65 ± 2.66	16.36 ± 2.55	0.10	(-0.65, 0.85)	0.791
Secondary efficacy endpoints							
	Baseline		**Week 2**				
	PF	BAK	PF	BAK	Difference	95% CI	*P*-value
8:00 AM	24.59 ± 2.30	24.24 ± 1.77	18.08 ± 2.64	17.43 ± 2.79	0.43	(-0.33, 1.19)	0.267
12:00 PM	24.37 ± 2.00	24.12 ± 1.90	17.54 ± 2.50	7.01 ± 2.78	0.39	(-0.36, 1.17)	0.313
4:00 PM	24.00 ± 1.98	23.65 ± 1.92	17.30 ± 2.41	16.76 ± 2.63	0.39	(-0.36, 1.14)	0.309
Diurnal	24.32 ± 1.94	24.00 ± 1.72	17.64 ± 2.42	17.07 ± 2.66	-	-	
	Baseline		**Week 6**				
	PF	BAK	PF	BAK	Difference	95% CI	*P*-value
8:00 AM	24.59 ± 2.30	24.24 ± 1.77	17.24 ± 2.42	16.89 ± 2.42	0.17	(-0.52, 0.86)	0.626
12:00 PM	24.37 ± 2.00	24.12 ± 1.90	16.88 ± 2.33	16.43 ± 2.48	0.35	(-0.37, 1.07)	0.338
4:00 PM	24.00 ± 1.98	23.65 ± 1.92	16.47 ± 2.35	16.33 ± 2.48	0.01	(-0.72, 0.74)	0.982
Diurnal	24.32 ± 1.94	24.00 ± 1.72	16.86 ± 2.27	16.55 ± 2.37	-	-	
	Baseline		**Week 12**				
	PF	BAK	PF	BAK	Difference	95% CI	*P*-value
12:00 PM	24.37 ± 2.00	24.12 ± 1.90	16.13 ± 2.42	15.95 ± 2.49	0.10	(-0.65, 0.84)	0.800
4:00 PM	24.00 ± 1.98	23.65 ± 1.92	15.91 ± 2.37	15.83 ± 2.49	-0.02	(-0.77, 0.74)	0.967
Diurnal	24.32 ± 1.94	24.00 ± 1.72	16.23 ± 2.41	16.05 ± 2.43	0.05	(-0.67, 0.78)	0.330

[a]PF minus BAK; [b]for all primary and secondary endpoints, the results were non-significant (*P* > 0.05). Abbreviations: PP, per protocol; CI, confidence interval; PF, preservative-free; BAK, benzalkonium chloride; IOP, intraocular pressure; mmHg, millimeter of mercury; %, percentage; SD, standard deviation; AM, ante meridiem or before midday; PM, post meridiem or after midday.

Table 3. Summary of adverse events for the safety population.

	PF latanoprost (N = 86)	BAK-preserved latanoprost (N = 84)
Deaths, n (%)	0 (0)	0 (0)
Serious AEs, n (%)	0 (0)	0 (0)
Discontinuation due to AEs, n (%)	1 (1.2)	0 (0)
Patients with ≥1 AE, n (%)	22 (25.6)	31 (36.9)
Total number of AEs, n (%)	39 (45.3)	45 (53.6)
OCULAR AEs, n (%)	**39 (48.1)**	**42 (51.9)**
Mild ocular AEs, n (%)	31 (79.5)	28 (66.7)
Blepharitis, n (%)	0 (0)	1 (2.4)
Eye redness, n (%)	1 (2.6)	2 (4.8)
Eye dryness, n (%)	3 (7.7)	3 (7.1)
Punctate keratitis, n (%)	0 (0)	1 (2.4)
Instillation site burning, n (%)	8 (20.5)	8 (19.1)
Itching, n (%)	0 (0)	2 (4.8)
Blurred vision, n (%)	3 (7.7)	3 (7.1)
Eye stinging, n (%)	4 (10.3)	2 (4.8)
Foreign body sensation, n (%)	4 (10.3)	4 (9.5)
Eye irritation, n (%)	2 (5.1)	2 (4.8)
Patient uncooperative, n (%)	2 (5.1)	0 (0)
Moderate ocular AEs, n (%)	8 (20.5)	14 (33.3)
Increased IOP, n (%)	8 (20.5)	8 (19.1)
No IOP control (≥22 mmHg), n (%)	0 (0)	1 (2.4)
Conjunctival hyperemia, n (%)	4 (10.3)	5 (11.9)
Severe ocular AEs, n (%)	0 (0)	0 (0)
SYSTEMIC AEs, n (%)	**0 (0)**	**3 (3.6)**
Mild systemic AEs, n (%)	0 (0)	2 (66.7)
Headache, n (%)	0 (0)	1 (33.3)
Skin erythema, n (%)	0 (0)	1 (33.3)
Moderate systemic AEs, n (%)	0 (0)	1 (33.3)
Periocular skin irritation, n (%)	0 (0)	1 (33.3)
Severe systemic AEs, n (%)	0 (0)	0 (0)

Abbreviations: N, number; %, percentage; AE, adverse event; BAK, benzalkonium chloride; IOP, intraocular pressure; PF, preservative-free.

Safety and tolerability

PF latanoprost and BAK-preserved latanoprost demonstrated comparable safety profiles. No serious treatment-related AEs (including deaths) were reported. One premature discontinuation due to ocular AEs was reported (IOP increased ≥22 mmHg) in the PF latanoprost treatment arm. The SP consisted of 86 patients in the PF latanoprost arm and 84 patients in the BAK-preserved latanoprost arm. In total, 39 AEs were reported in 22 patients in the PF latanoprost group (25.6%) and 45 AEs in 31 patients in the BAK-preserved latanoprost group (36.9%). The vast majority of AEs were ocular and had similar intensity and frequency between the two groups (Table 3). The most common ocular AEs were instillation site burning and increased IOP (≥22 mmHg), followed by conjunctival hyperemia, foreign body sensation, blurred vision, eye stinging, eye dryness, eye irritation, eye redness, and blepharitis. No significant observations were noted in slit-lamp biomicroscopy findings in visual acuity change from baseline and vital signs in any of the two treatment arms. Of the three systemic AEs reported in the BAK-preserved latanoprost treatment arm, two were mild and one was of moderate intensity.

DISCUSSION

This phase III, randomized, single-blind controlled study demonstrated the non-inferiority of a novel multi-dose PF latanoprost eye drop formulation compared to the BAK-preserved formulation in terms of reduction in IOP during a 12-week treatment period.

Both treatment groups showed a similar statistically significant mean decrease from baseline, in the study eye IOP, to the first assessment time-point (i.e., 2 weeks after treatment initiation), which was maintained for the entire duration of the study. Mean change in IOP from baseline up to 12 weeks ranged from -6.51 to -8.23 mmHg for the PF latanoprost group and from -6.8 to -8.16 for the BAK-preserved latanoprost group. The point estimate for the primary efficacy endpoint was 0.10 mmHg in the PP population, with the upper limit of the range of the optimal reduction in IOP not exceeding the non-inferiority margin of 1.5 mmHg. PF latanoprost and BAK-preserved latanoprost formulations also presented a comparable safety profile, with no serious treatment-related AEs being reported.

A clear trend has been observed over the last decade in the development and clinical use of PF ophthalmic solutions. Numerous clinical studies have demonstrated that switching from preserved to PF eye drops may alleviate ocular surface symptoms while maintaining efficacy at the same level [7, 8]. In the same vein, the substitution of preserved by PF topical antiglaucoma medications has been associated with an important increase in tear break-up time and amelioration of corneal staining and ocular surface disease index [6]. Therefore, published studies in the literature support the fact that PF prostaglandin ophthalmic solutions may present improved safety profiles concerning ocular-surface adverse events when compared to BAK-preserved solutions. BAK, the preservative used in latanoprost ophthalmic solution and the most commonly used ocular preservative, has been implicated in cases of ocular side effects, including conjunctival hyperemia. Previous studies have demonstrated that a high number of patients with glaucoma treated with topical eye drugs may have other underlying ocular surface diseases. In particular, as many as half of these patients appear to suffer from dry eye symptoms [17]. Furthermore, it has been suggested that extended exposure to BAK-preserved eye drops before filtering surgery may in some cases negatively affect surgical outcomes [18]. Based on these data, the emergence of a new generation of PF antiglaucoma medications is important, and BAK-free ophthalmic solutions should be available and used whenever required. Especially in patients suffering from pre-existing ocular surface diseases, or those with exposure to prolonged and concomitant preserved eye drop treatments, a condition that is often encountered in glaucoma patients, PF treatments could lead to better therapeutic adherence and potentially improve patients' quality of life [8].

The current study was designed to assess the non-inferiority of the test PF product in terms of efficacy parameters, namely reduction in IOP, compared to the control BAK-preserved product. The two products had a similar safety profile, with a slightly improved topical ocular tolerance of the PF formulation (i.e., fewer ocular AEs with lower severity and no systemic AEs). However, due to the current study setting, no conclusive evidence can be drawn in terms of safety, apart from the actual reporting of AEs recorded during the study.

Until recently, only preserved eye drop solutions of latanoprost have been available. The presence of BAK was deemed mandatory for preventing bacterial contamination of the solution; however, new techniques and devices are now available that warrant the safe deployment of PF eye drop solutions [19]. Indeed, PF latanoprost formulations are now available, and clinical data show that these ophthalmic solutions can alleviate potential ocular surface symptoms and improve patient compliance [20, 21]. As demonstrated by different phase II and phase III studies with the first PF latanoprost single-dose unit formulation (Monoprost; Laboratoires Théa, Clermont Ferrand, France), the efficacy of PF latanoprost was somewhat better than that of preserved latanoprost [6, 20].

Similarly, the present study demonstrated the non-inferiority of a new multi-dose PF latanoprost ophthalmic solution compared to the traditional multi-dose BAK-preserved latanoprost, in terms of IOP reduction. The percentage of IOP reduction observed from baseline to week 12 (32.3% for PF latanoprost and 32.51% for BAK-preserved latanoprost) was within the range of optimal IOP reduction (between -22% and -39%), which was also observed with other marketed PF latanoprost ophthalmic solutions [6, 8, 20, 21]. Similar reductions in IOP were observed for the two formulations throughout the duration of the study, with comparable efficacy at all intermediate time points, and a similar AE profile.

A potential limitation of the current study was the selection of a single morning IOP assessment as the primary endpoint for the comparison of the two formulations. However, this methodology is supported by several clinical arguments, including: i) the fact that in most patients with glaucoma, peak IOP generally occurs in the morning; ii) the plethora of previously published non-inferiority studies following the same methodology; and iii) preclinical and clinical studies indicating that the morning time point is the most challenging time to demonstrate non-inferiority in IOP between two formulations [9, 22]. Thus, it can be suggested that the IOP-lowering effect of PF latanoprost compared to the

BAK-preserved formulation can be extrapolated from the single morning IOP efficacy endpoint.

Another potential limitation was the single-blinded nature of the study, as lack of treatment masking could potentially influence patients' feelings regarding their treatment. A double-masked design might have been more appropriate, but this was not feasible because of the differences in the packaging systems between the two drugs; the investigational medicinal product is a PF preparation, which has a special container closure system. It should be noted, however, that the applied study procedures warranted that single masking was preserved and controlled by the study personnel, other than the principal investigator, and also by instructing study participants not to disclose information relevant to study treatment to the investigator.

Finally, a third limitation that can be considered was the rather short 12-week treatment period of the current study, which may not allow for an adequate investigation of the long-term side effects of the two latanoprost formulations. However, the current study setting was designed to allow for the assessment of the non-inferiority of the test PF product in terms of efficacy parameters (i.e., reduction in IOP) and to record the AE profiles of the two drugs. In this respect, the 12-week study period is a well-established treatment duration for topically applied prostaglandin analogs [6, 21].

Overall, the findings of the present study further confirmed that the IOP-lowering efficacy of latanoprost is not dependent on the presence of BAK, confirming previously reported results [6]. In fact, it has been suggested that BAK, through its detergent activity, may improve the effectiveness of topically applied drugs by enhancing their penetration into the eye and delivery into the cornea [17]. Indeed, PF prostaglandin-containing eye drops have shown decreased epithelial permeability and better maintenance of membrane integrity [22-24]. However, numerous clinical studies and meta-analyses have confirmed this claim by demonstrating equal IOP-lowering efficacy between PF and BAK-preserved prostaglandin analogs [6, 9, 17].

CONCLUSIONS

Taken together, the current study demonstrated the non-inferiority of PF latanoprost eye drops compared to BAK-preserved latanoprost eye drops in terms of IOP reduction, along with a good tolerability profile. The PF latanoprost 50 µg/mL formulation is a new multi-dose ophthalmic solution that may provide an efficacious alternative for glaucoma/ocular hypertension patients with existing ocular surface disease who do not tolerate eye drops with preservatives, especially when long-term treatment is required.

ETHICS DECLARATIONS

Ethical approval: The study protocol was prospectively approved by the National (Hellenic) Ethics Committee (NEC) (September 15, 2017) and the National (Hellenic) Organization for Medicines (EOF) (September 26, 2017). The study was conducted in compliance with the Declaration of Helsinki (2004) and Good Clinical Practice (GCP) guidelines. Relevant written informed consent was obtained from the patients prior to study enrollment. The study was registered in the EU Clinical Trials Register database with trial identification number 2017-002910-29.

Conflict of interests: The study sponsor participated in the study design and interpretation of the data, the writing of the report, and the decision to submit the paper for publication. Theodosiadis P., Konstas A.G., Halkiadakis I., Dimera V., Koufakis D., Georgakopoulos K., and Kanonidou E. were investigators in the study, participated in the conduct of the study, and in the review and approval of the manuscript.

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